



MTHFR gene

methylenetetrahydrofolate reductase

Normal Function

The *MTHFR* gene provides instructions for making an enzyme called methylenetetrahydrofolate reductase. This enzyme plays a role in processing amino acids, the building blocks of proteins. Methylenetetrahydrofolate reductase is important for a chemical reaction involving forms of the vitamin folate (also called vitamin B9). Specifically, this enzyme converts a molecule called 5,10-methylenetetrahydrofolate to a molecule called 5-methyltetrahydrofolate. This reaction is required for the multistep process that converts the amino acid homocysteine to another amino acid, methionine. The body uses methionine to make proteins and other important compounds.

Health Conditions Related to Genetic Changes

anencephaly

Several variations (polymorphisms) in the *MTHFR* gene have been associated with an increased risk of neural tube defects, a group of birth defects that occur during the development of the brain and spinal cord. Anencephaly is one of the most common types of neural tube defect. Affected individuals are missing large parts of the brain and have missing or incompletely formed skull bones.

The most well-studied polymorphism related to neural tube defects changes a single DNA building block (nucleotide) in the *MTHFR* gene. Specifically, it replaces the nucleotide cytosine with the nucleotide thymine at position 677 (written as 677C>T). This common variant results in a form of methylenetetrahydrofolate reductase that has reduced activity at higher temperatures (thermolabile). People with the 677C>T polymorphism, particularly those with two copies of the genetic change, have elevated levels of homocysteine in their blood resulting from the reduced activity of methylenetetrahydrofolate reductase.

Researchers have studied *MTHFR* gene polymorphisms in individuals with neural tube defects and in their mothers, but it remains unclear how these variations could affect the developing brain and spinal cord. The increased risk of neural tube defects may be related to differences in the ability of methylenetetrahydrofolate reductase to process folate; a shortage of this vitamin is an established risk factor for neural tube defects.

Although *MTHFR* gene polymorphisms are associated with an increased risk of neural tube defects, these variations are common in many populations worldwide. Most people with *MTHFR* gene polymorphisms do not have neural tube defects, and

their children are also typically unaffected. Changes in the *MTHFR* gene are only one of many genetic and environmental factors that are thought to contribute to these complex conditions.

homocystinuria

At least 40 mutations in the *MTHFR* gene have been identified in people with homocystinuria, a disorder in which the body is unable to process homocysteine and methionine properly. People with this condition often develop eye problems, abnormal blood clotting, skeletal abnormalities, and cognitive problems. Most of the mutations that cause homocystinuria change single amino acids in methylenetetrahydrofolate reductase. These changes impair the function of the enzyme, and some cause the enzyme to be turned off (inactivated). Other mutations lead to the production of an abnormally small, nonfunctional version of the enzyme. Without functional methylenetetrahydrofolate reductase, homocysteine cannot be converted to methionine. As a result, homocysteine builds up in the bloodstream, and the amount of methionine is reduced. Some of the excess homocysteine is excreted in urine (homocystinuria). Researchers have not determined how altered levels of homocysteine and methionine lead to the various health problems affecting multiple parts of the body in people with homocystinuria.

spina bifida

Polymorphisms in the *MTHFR* gene are also associated with an increased risk of spina bifida, another common type of neural tube defect. In people with this condition, when the spine forms, the bones of the spinal column do not close completely around the developing nerves of the spinal cord. As a result, part of the spinal cord may protrude through an opening in the spine, leading to permanent nerve damage.

As described above, variations in the *MTHFR* gene may increase the risk of neural tube defects by changing the ability of methylenetetrahydrofolate reductase to process folate. However, these variations are common in many populations worldwide. Most people with *MTHFR* gene polymorphisms do not have neural tube defects, nor do their children.

other disorders

Polymorphisms in the *MTHFR* gene have also been studied as possible risk factors for a variety of common conditions. These include heart disease, stroke, high blood pressure (hypertension), high blood pressure during pregnancy (preeclampsia), an eye disorder called glaucoma, psychiatric disorders, and certain types of cancer. Research indicates that individuals who have the 677C>T polymorphism on both copies of the *MTHFR* gene have an increased risk of developing vascular disease, including heart disease and stroke. The 677C>T polymorphism has also been suggested as a risk factor for cleft lip and palate, a birth defect in which there is a split in the upper lip and an opening in the roof of the mouth. Many of the *MTHFR* gene

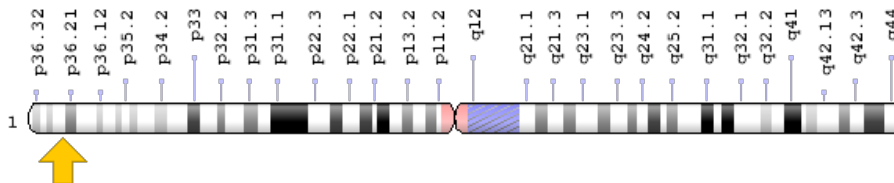
polymorphisms alter or decrease the activity of methylenetetrahydrofolate reductase, leading to an increase of homocysteine in the blood. This increase in homocysteine levels may contribute to the development of many of these conditions.

Studies of *MTHFR* gene variations in people with these disorders have had mixed results, with associations found in some studies but not in others. Therefore, it remains unclear what role changes in the *MTHFR* gene play in these disorders. It is likely that additional factors influence the processing of homocysteine and that variations in homocysteine levels play a role in whether a person develops any of these conditions. A large number of genetic and environmental factors, most of which remain unknown, likely determine the risk of developing most common, complex conditions.

Chromosomal Location

Cytogenetic Location: 1p36.22, which is the short (p) arm of chromosome 1 at position 36.22

Molecular Location: base pairs 11,785,730 to 11,806,103 on chromosome 1 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- 5,10-methylenetetrahydrofolate reductase
- 5,10-methylenetetrahydrofolate reductase (NADPH)
- methylenetetrahydrofolate reductase (NAD(P)H)
- MTHR_HUMAN

Additional Information & Resources

Educational Resources

- Madame Curie Bioscience Database: Molecular Biology of Methylenetetrahydrofolate Reductase (MTHFR) and Overview of Mutations/Polymorphisms
<https://www.ncbi.nlm.nih.gov/books/NBK6561/>

Genetic Testing Registry

- GTR: Genetic tests for MTHFR
<https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=4524%5Bgeneid%5D>

Scientific articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28MTHFR%5BTI%5D%29+OR+%285,10-methylenetetrahydrofolate+reductase%5BTI%5D%29%29+AND+%28%285,10-methylenetetrahydrofolate+reductase+%28nadh%29%29+OR+%28methylene-thf+reductase+%28nadh%29%29+OR+%28methylenetetrahydrofolate+reductase+%28nadh2%29%29+OR+%28methylenetetrahydrofolate+reductase%5BMAJR%5D%29+OR+%28methylenetetrahydrofolate+reductase%5BMAJR%5D%29+OR+%28methylenetetrahydrofolate+reductase+%28nadh%29%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+360+days%22%5Bdp%5D>

OMIM

- 5,10-METHYLENETETRAHYDROFOLATE REDUCTASE
<http://omim.org/entry/607093>

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
<http://atlasgeneticsoncology.org/Genes/MTHFRID41448ch1p36.html>
- ClinVar
<https://www.ncbi.nlm.nih.gov/clinvar?term=MTHFR%5Bgene%5D>
- HGNC Gene Symbol Report
http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=7436
- NCBI Gene
<https://www.ncbi.nlm.nih.gov/gene/4524>
- UniProt
<http://www.uniprot.org/uniprot/P42898>

Sources for This Summary

- Bhargava S, Ali A, Parakh R, Saxena R, Srivastava LM. Higher incidence of C677T polymorphism of the MTHFR gene in North Indian patients with vascular disease. *Vascular*. 2012 Apr;20(2):88-95. doi: 10.1258/vasc.2011.0a0320. Epub 2012 Feb 28.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/22375042>
- Botto LD, Yang Q. 5,10-Methylenetetrahydrofolate reductase gene variants and congenital anomalies: a HuGE review. *Am J Epidemiol*. 2000 May 1;151(9):862-77. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/10791559>
- Khandanpour N, Willis G, Meyer FJ, Armon MP, Loke YK, Wright AJ, Finglas PM, Jennings BA. Peripheral arterial disease and methylenetetrahydrofolate reductase (MTHFR) C677T mutations: A case-control study and meta-analysis. *J Vasc Surg*. 2009 Mar;49(3):711-8. doi: 10.1016/j.jvs.2008.10.004. Epub 2009 Jan 21. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/19157768>
- Kumar A, Kumar P, Prasad M, Sagar R, Yadav AK, Pandit AK, Jali VP, Pathak A. Association of C677T polymorphism in the methylenetetrahydrofolate reductase gene (MTHFR gene) with ischemic stroke: a meta-analysis. *Neurol Res*. 2015 Jul;37(7):568-77. doi: 10.1179/1743132815Y.0000000008. Epub 2015 Jan 16.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/25591425>
- Moll S, Varga EA. Homocysteine and MTHFR Mutations. *Circulation*. 2015 Jul 7;132(1):e6-9. doi: 10.1161/CIRCULATIONAHA.114.013311. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/26149435>
- Sibani S, Christensen B, O'Ferrall E, Saadi I, Hiu-Tim F, Rosenblatt DS, Rozen R. Characterization of six novel mutations in the methylenetetrahydrofolate reductase (MTHFR) gene in patients with homocystinuria. *Hum Mutat*. 2000;15(3):280-7.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/10679944>
- Trabetti E. Homocysteine, MTHFR gene polymorphisms, and cardio-cerebrovascular risk. *J Appl Genet*. 2008;49(3):267-82. doi: 10.1007/BF03195624. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/18670064>
- Trimmer EE. Methylenetetrahydrofolate reductase: biochemical characterization and medical significance. *Curr Pharm Des*. 2013;19(14):2574-93. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/23116396>
- Urreiziti R, Moya-García AA, Pino-Ángeles A, Cozar M, Langkilde A, Fanhoe U, Esteves C, Arribas J, Vilaseca MA, Pérez-Dueñas B, Pineda M, González V, Artuch R, Baldellou A, Vilarinho L, Fowler B, Ribes A, Sánchez-Jiménez F, Grinberg D, Balcells S. Molecular characterization of five patients with homocystinuria due to severe methylenetetrahydrofolate reductase deficiency. *Clin Genet*. 2010 Nov;78(5):441-8. doi: 10.1111/j.1399-0004.2010.01391.x.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/20236116>
- Xie SZ, Liu ZZ, Yu JH, Liu L, Wang W, Xie DL, Qin JB. Association between the MTHFR C677T polymorphism and risk of cancer: evidence from 446 case-control studies. *Tumour Biol*. 2015 Nov; 36(11):8953-72. doi: 10.1007/s13277-015-3648-z. Epub 2015 Jun 17.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/26081619>
- Yadav U, Kumar P, Yadav SK, Mishra OP, Rai V. "Polymorphisms in folate metabolism genes as maternal risk factor for neural tube defects: an updated meta-analysis". *Metab Brain Dis*. 2015 Feb; 30(1):7-24. doi: 10.1007/s11011-014-9575-7. Epub 2014 Jul 9. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/25005003>

- Yan L, Zhao L, Long Y, Zou P, Ji G, Gu A, Zhao P. Association of the maternal MTHFR C677T polymorphism with susceptibility to neural tube defects in offsprings: evidence from 25 case-control studies. PLoS One. 2012;7(10):e41689. doi: 10.1371/journal.pone.0041689. Epub 2012 Oct 3.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/23056169>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3463537/>
- Zhang T, Lou J, Zhong R, Wu J, Zou L, Sun Y, Lu X, Liu L, Miao X, Xiong G. Genetic variants in the folate pathway and the risk of neural tube defects: a meta-analysis of the published literature. PLoS One. 2013 Apr 4;8(4):e59570. doi: 10.1371/journal.pone.0059570. Print 2013.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/23593147>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3617174/>

Reprinted from Genetics Home Reference:

<https://ghr.nlm.nih.gov/gene/MTHFR>

Reviewed: April 2016

Published: January 24, 2017

Lister Hill National Center for Biomedical Communications

U.S. National Library of Medicine

National Institutes of Health

Department of Health & Human Services